Risk Management Option Analysis Conclusion Document

Substance Name: 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylindeno[5,6-c]pyran (HHCB)

EC Number: 214-946-9

CAS Number: 1222-05-5

Authority: France

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Foreword

The purpose of Risk Management Option analysis (RMOA) is to help authorities decide whether further regulatory risk management activities are required for a substance and to identify the most appropriate instrument to address a concern.

RMOA is a voluntary step, i.e., it is not part of the processes as defined in the legislation. For authorities, documenting the RMOA allows the sharing of information and promoting early discussion, which helps lead to a common understanding on the action pursued. A Member State or ECHA (at the request of the Commission) can carry out this case-by-case analysis in order to conclude whether a substance is a 'relevant substance of very high concern (SVHC)' in the sense of the SVHC Roadmap to 2020[1].

An RMOA can conclude that regulatory risk management at EU level is required for a substance (e.g. harmonised classification and labelling, Candidate List inclusion, restriction, other EU legislation) or that no regulatory action is required at EU level. Any subsequent regulatory processes under the REACH Regulation include consultation of interested parties and appropriate decision making involving Member State Competent Authorities and the European Commission as defined in REACH.

This Conclusion document provides the outcome of the RMOA carried out by the author authority. In this conclusion document, the authority considers how the available information collected on the substance can be used to conclude whether regulatory risk management activities are required for a substance and which is the most appropriate instrument to address a concern. With this Conclusion document the Commission, the competent authorities of the other Member States and stakeholders are informed of the considerations of the author authority. In case the author authority proposes in this conclusion document further regulatory risk management measures, this shall not be considered initiating those other measures or processes. Since this document only reflects the views of the author authority, it does not preclude Member States or the European Commission from considering or initiating regulatory risk management measures which they deem appropriate.

[1] For more information on the SVHC Roadmap: http://echa.europa.eu/addressing-chemicals-of-concern/substances-of-potential-concern/svhc-roadmap-to-2020-implementation

1. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Table: Completed or ongoing processes

RMOA	☐ Risk Management Option Analysis (RMOA) other than this RMOA	
REACH Processes	Evaluation	☒ Compliance check, Final decision
		☐ Testing proposal
		☐ CoRAP and Substance Evaluation
	Authorisation	☐ Candidate List
		☐ Annex XIV
	Restri -ction	☐ Annex XVII[2]
Harmonised C&L	☐ Annex VI (CLP) (see section 3.1)	
Processes under other EU legislation	☐ Plant Protection Products Regulation Regulation (EC) No 1107/2009	
	☐ Biocidal Product Regulation Regulation (EU) 528/2012 and amendments	
Previous legislation	☐ Dangerous substances Directive Directive 67/548/EEC (NONS)	
	☒ Existing Substances Regulation Regulation 793/93/EEC (RAR/RRS)	
(UNEP) Stockholm convention (POPs Protocol)	☐ Assessment	
	☐ In relevant Annex	

[2] Please specify the relevant entry.

Other processes/ EU legislation	☒ Other (provide further details below)

A risk assessment report of the substance HHCB has been prepared by the Netherlands in the context of Council Regulation (EEC) No. 793/93 on the evaluation and control of existing substances (Final version, May 2008). It has been concluded that there is no need for risk reduction measures beyond those which are being applied already (conclusion (ii)) both for the Environment and human health.
Furthermore, in the RAR published in 2008 the Netherlands concluded that HHCB does not meet the criteria for PBT substances. This point is currently under discussion based on new data available which allow a re-assessment of the PBT properties of this substance.
In addition, a compliance check has been adopted the 31st of October 2018 with the following requirements:
1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: OECD TG 414) in a second species (rabbit), oral route with the registered substance;
2. Extended one-generation reproductive toxicity study (Annex X, Section A.7.3.i test method: OECD TG 443) in rats, oral route with the registered substance specified as follows:

- Ten weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce systemic toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation.

The requested information has to be submitted in an updated registration dossier by 7 May 2021.

Regarding other regulatory framework, HHCB has been evaluated by the SCCNFP (Scientific Committee on Cosmetic products and Non-Food Products intended for consumers) for its use as fragrance ingredient in cosmetic products (SCCNFP/0610/02, final report, 17 September 2002). SCCNFP was of the opinion that HHCB can be safely used in cosmetics without any restriction for its use. Other sources of consumer exposure from non food products (e.g. laundry products) have not been considered.

2. CONCLUSION OF RMOA

This conclusion is based on the REACH and CLP data as well as other available relevant information taking into account the SVHC Roadmap to 2020, where appropriate.

Conclusions	**Tick box**
Need for follow-up regulatory action at EU level:	
Harmonised classification and labelling	
Identification as SVHC (authorisation)	
Restriction under REACH	
Other EU-wide regulatory measures	X
Need for action other than EU regulatory action	

No action needed at this time	

3. NEED FOR FOLLOW-UP REGULATORY ACTION AT EU LEVEL

Data on endocrine properties of HHCB in vertebrates is limited to some in vitro and in vivo mechanistic studies (OECD level 2 and 3).

An endocrine activity has been observed on ER pathway. Several in vitro studies report a weak agonist activity on ERα and an antagonist activity on ERβ. In short-term exposure tests performed on fish, HHCB induced the VTG mRNA expression in adult male medaka, indicating an estrogenic effect. In contrast, only anti-estrogenic activity of HHCB was observed in juvenile ERE-luciferase transgenic zebrafish exposed for 96 h. The in vivo results support these in vitro findings, and highlight the differential capacity of HHCB to interfere with ER signalling. Albeit an alert on ER signalling could be identified, information on HHCB effects on reproduction and development of the fish would be needed to draw a firm conclusion about the HHCB (anti)estrogenic effects.

Regarding other signaling pathways, the available data are not sufficient to conclude. There is no sufficient information on AR signaling pathway. There is no alert on TR signalling pathway, but additional studies would be required to conclude. In addition, an alert on steroidogenic activity has been identified, but information are requested to confirm the observed effect.

Regarding the vertebrate toxicity related to human and environmental health, there is a lack of information on reproductive and developmental toxicity. Based on the one in vivo test measuring only one endpoint (Seinen et al., 1999), it is not possible to conclude whether or not HHCB displays endocrine adverse effects.

Contrasting with vertebrates, the reproductive toxicity of HHCB on invertebrates has been evidenced in several studies. These studies highlight the possible ED properties of HHCB identified in arthropods, worms and molluscs. However, based on current knowledge, no biological plausible link can be established between a reproductive adverse effect in invertebrates and an endocrine mode of action, as this is required for the identification of an ED based on the EU definition and criteria (Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009).

In this context, further investigations are needed, particularly on long-term reproductive and developmental toxicity in vertebrates (rodent and/or fish) and on endocrine mechanisms in invertebrate species, to assess the ED properties of HHCB. A compliance check (CCH) is currently proposed by ECHA, which requires a pre-natal developmental toxicity study (OECD TG 414) and an extended one-generation reproductive toxicity study (OECD TG 443), with cohorts 1A and 1B (with extension to mate the Cohort 1B animals to produce the F2 generation). These studies may provide useful information to state on the ED long-term effects for human health. Depending on the outcomes of the CCH, and after evaluating the new dataset, other studies could be considered. Further work on environmental health within substance evaluation would be necessary to clarify the concern on endocrine effects in fish.

Regarding PBT properties, the substance has been assessed under the previous legistation by Netherlands. The EU-RAR (2008) associated to this assessment concluded that HHCB is not PBT. However, there is a need to reassess the PBT properties of the substance based on new methods and data available. No conclusions is made at this stage by FR-MSCA.

FR-MSCA intends to put HHCB in the CoRAP for evaluation, in order to clarify the concerns regarding ED and PBT.

In addition, there might be an interest having a group approach on the "musk" family compounds that present similarities of effects. In the past, France screened the similar substance OTNE. As a group approach for EDT and PBT properties would require substantial resources, ECHA could usefully prepare an identification of potential group members and an overview of the needed work and coordinate that work with the voluntary Member States willing to contribute on this topic.

4. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS IF NECESSARY

Follow-up action	Date for follow-up	Actor
Substance Evaluation	2021 or 2022	France